Risk of Kidney Tumours in Firemen

STUDIES AND RESEARCH PROJECTS

Douglas B. McGregor

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REPORT

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Kidney tumours	1
Firemen: general characteristics and exposures	3
Studies reviewed	4
Discussion	8
Conclusion	11
References	12
Table 1	19

Kidney Tumours

Cancers involving the kidney may be primary or secondary. Although the kidney is a relatively common site of metastasis, secondary lesions usually are asymptomatic and discovered during post mortem examination. Renal cell carcinoma is the most common malignant lesion of the kidney, accounting for approximately 85% of all renal cancers. The vast majority of these tumours are adenocarcinoma. Renal pelvis tumours are the second most frequent type and account for 7 to 8% of all kidney tumours, although in patients with Balkan endemic familial nephropathy renal pelvic neoplasms account for almost 50% of all renal tumours. Over 90% of renal pelvic tumours are classified as transitional cell carcinoma and are virtually identical to the tumours in the ureter and urinary bladder. Other types tumours found in the kidney include nephroblastoma (i.e., Wilms' tumour), which is usually diagnosed before age 5 and accounts for 5 to 6% of kidney malignancies, and various sarcomas of renal origin. Renal cell carcinoma, often bilateral, is observed in more than two-thirds of patients with von Hippel-Lindau disease, an autosomal dominant diasease, characterized by retinal angiomas and haemangioblastomas of the central nervous system (Horton et al., 1976, Nelson et al., 1994).

Kidney cancer is the 15th most common cancer world-wide and it is the 6th most frequent in western Europe, being particularly high in the Bas-Rhin region of France, in the Czech Republic and in Scandinavian countries. The incidence is lower among Asians and Africans. Close to 190,000 cases are diagnosed annually and more than 90,000 patients die of the disease each year (Ferlay et al., 2001). In 1999 in the USA, renal cancers were diagnosed in approximately 30,000 patients, which included 17,800 deaths (Landis et al., 1999). The incidence of primary renal cell carcinoma seems to have increased slowly over the past 20 years by 2 to 4% per year (Chow et al., 1999). The male-to-female ratio for both renal cell carcinoma and tumours of the renal pelvis is 2:1. Most cases of renal cell carcinoma and tumours of the renal pelvis occur in people of between 50 and 70 years of age, but renal cell carcinoma has been observed even in neonates. The 5-year survival rate is approximately 50%.

Among the better-established risk factors identified by epidemiology for kidney cancer are cigarette smoking, obesity and hypertension. The association of tobacco

smoking with cancers of the urinary system was first established for transitional cell carcinoma of the bladder, but it has now been extended to renal cell carcinomas (McLaughlin et al., 1984; IARC, 1986), the risk increasing two-fold in heavy smokers (Doll, 1996). Being over-weight or obese has been shown to increase the risk of renal cell cancer in a dose-related manner in both men and women (Calle et al., 2003). For men (since by far the majority of firemen are men), the data from this recent, prospective cohort of 404,576 men in the USA found that the risks associated with four body mass index (BMI)[1] categories were:

BMI	18.5-24.9	25.0-29.9	30.0-34.9	35.0-39.9
RR (95% CI)	1.00(-)	1.18 (1.02-1.37)	1.36 (1.06-1.74)	1.70 (0.99-2.92)

A review of 19 studies found that, in all but one, there was more than a 2-fold increase in renal cell carcinoma risk in obese men and women (IARC, 2002). Men with a low BMI at age 20 years but who gained weight up to 50 years had moderately increased risk (IARC, 2002). A population attributable risk of 25% has been estimated for a BMI of > 25 versus BMI < 25 (Yu et al., 1986; Bergström et al., 2001). However, the results of the few published studies on the association between physical activity and renal cell carcinoma are inconsistent and do not permit an evaluation to be made (IARC, 2002).

Diabetes and hypertension (the latter independent of obesity) are also important risk factors for renal cell carcinoma (Yuan et al., 1998; Chow et al., 2000). Grossman et al., 2002, reviewed 13 case-control studies, including 6964 cases of renal cell cancer and 9181 controls, and found that the adjusted odds ratio for renal cell cancer among patients with hypertension, relative to those who do not, was 1.75 (1.61-1.90). No clear association was found between hypertension and cancer of other sites. Certain diuretics may be used in management of hypertension or weight reduction, as well as kidney-damaging analgesics such as phenacetin, can also increase the incidence of kidney cancers. An influence of beverages such as coffee and alcohol has not been clearly determined, despite many studies (WHO, 2003). A hormonal basis for renal cell cancer was suggested by work on prolonged administration of oestrogen to male Syrian hamsters, although similar data have not been reported in humans (Harris 1983).

Studies relating occupational exposures to kidney cancer have been largely contradictory. Several studies showed an increased risk of kidney cancer in workers who were exposed to asbestos (Selikoff et al., 1979; Enterline et al., 1987; Maclure, 1987). For other occupational exposures, the data have been less consistent, e.g., lead. Steenland & Boffetta (2000) reviewed the cancer epidemiology of lead as described in eight studies of either cancer mortality or cancer incidence among highly exposed workers; most of which were cohort studies of lead smelter or battery workers exposed decades ago. These studies provide little evidence of increased risk of kidney cancer (combined RR = 1.01, 0.72-1.42, 40 observed) although two studies did show a two-fold increase in kidney cancer. In addition, there have been unconfirmed associations of renal cancer with other occupational exposures such as coke oven emissions (Redmond et al., 1972), polycyclic aromatic hydrocarbons in general (Nadon et al., 1995), gasoline (reviewed by McLaughlin, 1993), aluminium (Andersen et al., 1982) and leather tanners, shoe workers, dry cleaners and exposure

[1] BMI = Body Mass Index = Body weight in Kg/(Body height in M)^2

to trichloroethylene (WHO, 2003). These are often quoted in the epidemiological literature on firemen as exposures that could increase the risk of several cancers, including those of the kidney, but the primary evidence is often weak. In a cohort of 1629 leather tanners in Sweden, eight cases of kidney cancer were observed, while 3.4 would have been expected from regional rates (Malker et al., 1984). The hypothesis of this association was not supported by another study (Acheson et al., 1984). As summarised by IARC, the occurrence of cancer of the kidney was generally not elevated in cohort studies (the main ones being 3 in the USA and one in Sweden); however, a study of German workers exposed to trichloroethylene revealed five cases of renal cancer whereas no case was found in an unexposed comparison group. This study may, however, have been initiated after the observation of a cluster. A case–control study and a multi-site cancer study, both from Montréal, Canada, provided discordant results with regard to cancer of the kidney (IARC, 1995). The aluminium smelters study by Andersen et al., 1982 was a study of cancer incidence and mortality in 7410 male employees in primary aluminium production in Norway during the period 1953–1979. For cancer incidence, expected figures were computed on the basis of five-year, age-specific regional incidence; for mortality, national rates were used. The observed number of cases exceeded that expected for several cancers, including kidney, but only for cancer of the lung was the excess statistically significant. In a later study in the same industry, however, an association was found between incidence of kidney cancer and exposure to heat stress 20 – 35 years before observation (Ronneberg & Andersen, 1995). Clearly, the implication that heat stress might be a risk factor, particularly after a long lag period, is interesting in the context of evaluating risks for firemen, but the study requires confirmation. Other factors that might be encountered by firemen and have been mentioned as associated with kidney cancer include nitrosamines and cadmium, but on the basis of little evidence.

Firemen: General Characteristics and Exposures

Fighting fires is a mentally and physically demanding occupation in which burns, falls and crush injuries are commonplace and exposure to smoke and other airborne organic and inorganic substances is taken for granted (Gochfeld, 1995). The largest category of non-fatal fire fighter injuries associated with fires has been reported to be contact with flames and smoke (39%) and the leading cause of non-fatal injury among younger firemen is related to smoke inhalation (FEMA, 1990). Approximately 90% of structural fires are either extinguished or abandoned and fought from outside within 5 – 10 min., the average duration of heavy physical activity being 10 min. (Gilman & Davis, 1993).

The task of fire fighting consists of two phases: (1) *knockdown*, during which the fire is brought under control, and (2) *overhaul*, when the fire is extinguished and clean up begins. Although self-contained breathing apparatus (SCBA)s are available, these are seldom worn from the time the firemen arrive at the scene until the time that they leave. In a study of exposures in the City of Montréal fire department, Austin et al., 2001a, found that SCBAs were worn about 50% of the time at structural fires, but they were worn for only 6% of the total time spent at all types of fires. Masks are generally put on when the firemen enter a fire or "see smoke," but it is difficult for them to judge when the mask can be safely removed and they are rarely worn during the smouldering phase of a fire or during mop-up operations. Furthermore, communication is essential and this is difficult with the mask in place.

It is recognised that during overhaul, recommended ceiling or short-term exposure levels can often be exceeded, e.g., for acrolein, benzene, carbon monoxide, formaldehyde, glutaraldehyde, nitrogen dioxide and sulphur dioxide (Bolstad-Johnson et al., 2000). Several toxic materials, e.g., carbon monoxide and benzene, were found to be present at appreciable concentrations in the atmosphere at real fire scenes when SCBAs were only used part of the time or not at all, owing to the impression that there was low smoke intensity (Brandt-Rauf et al., 1988, 1989). In a study of municipal structural fires, Austin et al., 2001b found that the spectra of volatile organic compounds were similar and remarkable for their simplicity, being dominated by benzene along with toluene and naphthalene. They also found that propylene and 1,3-butadiene were present in all of the fires and that styrene and other alkylated benzenes were frequently identified. Indeed, just 14 different compounds accounted for about 75% of the total volatile organic materials measured. These same compounds constituted approximately 65% of all volatile organic compounds in experimental fires burning various materials commonly found in structural fires (Austin et al., 2001c). None of these compounds has been implicated as human kidney carcinogens. Other materials that have quantified with some regularity include acrolein, carbon monoxide, formaldehyde, glutaraldehyde, hydrogen chloride, hydrogen cyanide and nitrogen dioxide (Bolstad-Johnson et al., 2000; Caux et al., 2002). There may also be exposure to asbestos and various metals, such as cadmium, chromium and lead. In addition, there is almost certainly exposure to diesel exhaust and fumes and to polycyclic aromatic hydrocarbons (PAHs). However, neither PAHs (Nadon et al., 1995) nor diesel exhausts and fumes (IARC, 1989) have been implicated as risk factors for human kidney cancer.

Studies Reviewed.

There have been many studies of mortality amongst firemen, but only a few have specifically identified kidney as a possible target for carcinogenesis. These (eight) studies are reviewed here. Because of the heterogeneity of the studies, it was considered inappropriate to attempt any overall quantitative assessment, so this review is confined to a qualitative evaluation of the available evidence.

A historical cohort was assembled of all firemen employed between 1927 and 1987 in Edmonton and Calgary, Alberta (Guidotti, 1993). Even short employment periods (< 1 year) were justified on the grounds that much of the first year is in training with considerable exposure to smoke and the use of apparatus. An exposure opportunity index term, reflecting estimates of the relative time spent in close proximity to fires by job classification, was applied to refine exposure data based on years of service. The applied weightings were: fireman lieutenant and captain = 1.0; safety or training officer = 0.2; district chief or volunteer fireman = 0.1; desk job and other posts not involving active fire fighting = 0.0. The firemen were followed for 64983 person-years and the vital status determined for 3193, which included 370 deaths, 92 being due to cancer. This provided a significantly increased risk for all cancers, standardised mortality ratio (SMR) = 1.14 (1.02-1.55)[1] based on the 92 cases. For cancers of the kidney and ureter combined, SMR = 4.14 (1.66-8.53) based on 7 cases. All cases were seen in men entering the fire service before 1915 or after 1950. The earliest case appeared 18 years after entry, the maximum risk occurring 40-49 years

[1] risk ratio (95% confidence interval)

after entry. The frequency appeared to increase with increasing duration of employment and (weighted) exposure opportunity, although one of the 7 cases was observed in a worker without fire fighting experience.

A cohort study of 5414 firemen in metropolitan Toronto, Ontario was conducted on all employees who had worked for at least 6 months at any time between 1950 and 1989 (Aronson et al., 1994; same data also reported in L'Abbé & Thomlinson, 1992). Deaths and causes of deaths were obtained by computerised record linkage. There were 114008 person-years of follow-up. The average years of follow-up and years of employment were 21 and 20, respectively. The incidence of all cancers combined was not elevated, SMR = 1.05 (0.91-1.20) based on 199 cases. The SMR for kidney and ureter cancers was 0.43 (0.05-1.56) based on 2 cases. Portions of the data were also analysed after stratification according to years since first exposure and years of employment, but the kidney cancer data were too meagre for this analysis to be performed.

Tornling et al., 1994, studies cancer incidence and mortality in firemen who had been working with fire fighting methods used in Sweden from the beginning of the 20th century onwards. Firemen employed for at least one year in the City of Stockholm during the period 1931 to 1983 were traced and an index of the number of fires fought was calculated for each individual. Overall cancer incidence for 1958 to 1986 was equal to the expected, SMR = 1.00 (0.83-1.19) based on 127 cases and kidney cancer was less frequent than expected, but not significantly so, SMR = 0.36 (0.04-1.29) based on only 2 cases. Overall cancer mortality also was close to the expected value, SMR = 1.02 (0.88-1.25) based on 93 cases, as was kidney cancer mortality, SMR = 1.10 (0.30-2.81). It is noted that, in this study, the category of high number of runs was > 1000, which would be in the low runs category in the Philadelphia firemen study described below (Baris et al., 2001).

A particularly large investigation made into the occurrence of cancer death in firemen was that of Burnett et al., 1994, which unfortunately was reported only as a brief communication (although full details are available from the authors). This was a proportionate mortality study of white firemen in 27 states of the USA from 1984 through 1990, using data from the National Occupational Mortality Surveillance system. There were 5744 deaths, 1636 being due to cancer. The proportionate mortality ratio (PMR) was statistically significantly increased for all cancers combined, PMR = 1.10 (1.06-1.14) and for that portion of the cases who died at < 65 years of age, PMR = 1.12 (1.04-1.21). For all kidney cancer deaths the PMR = 1.44 (1.08-1.89) based on 53 deaths and for those that died at age <65 years, the PMR = 1.41 (0.90-2.10) based on 24 cases. These elevations that were significant or of boarder-line significance were based on numbers kidney cancer cases substantially higher than those normally encountered in studies on firemen. The strength of this study is its very large numbers of cancer deaths. Its weaknesses (shared by other studies of this type) were listed by the authors and, because they apply to any study of this type, are listed in the Discussion section.

A related study was that of Ma et al., 1998, who used a database overlapping that of Burnett et al., 1994, but their stated objective was to examine possible racial differences in susceptibility to cancer mortality. Furthermore, although the database was extended by three years to 1993, data were lost because three states were

removed from consideration (Alaska, New York and Pennsylvania). There were 6607 deaths, 1817 being due to cancer. Although the stated objective was a racial comparison, there were only 66 cancer deaths amongst blacks, while there were 1817 amongst whites. For all cancers combined amongst whites, the mortality odds ratio (MOR) = 1.1 (1.1-1.2) based on 1817 deaths, while amongst blacks the MOR = 1.2 (0.9-1.5) based on 66 deaths. For kidney cancer deaths amongst whites, the MOR = 1.3 (1.0-1.7) based on 49 deaths, while no cases of kidney cancer were recorded amongst blacks. The likely large degree of overlap with the Burnett et al., 1994 study indicates that these cannot be considered as independent investigations of kidney cancer.

Delahunt et al., 1995 conducted a case-control study of renal cell carcinoma using data reported in the New Zealand Cancer Registry from 1978 to 1986 inclusive. The occupational risk for renal cell carcinoma was derived by comparison of 710 renal cell carcinoma cases with the occupation of 12,756 cases of non-urinary tract malignancies reported in the Registry over the same period. The relative risk (RR) for firemen was 3.51 (2.09-5.92). After stratification of the data by smoking history and age revealed an increased RR of 4.69 (2.47-8.93). The main advantage of using other cancers as controls is information bias is minimised and selection bias due to incomplete cancer registration is reduced. A potential disadvantage is the possibility of introducing selection bias if the (occupational) exposure under consideration is associated with an increased risk of cancer at other sites. The effect of such bias, however, is to reduce the apparent risk.

Bates et al., 2001 made a historical cohort study of all paid firemen in New Zealand from 1977 to 1995. The data were obtained from a registry of all firemen maintained by the United Fire Brigades Association of New Zealand (UFBA), principally for confirming eligibility for long-service awards. The study cohort was defined as every person in the UFBA database who had worked as a fireman for at least one year and who had been paid for at least one day in the study period. Anonymous cancer and mortality data came from the New Zealand Health Information Service. General population data, by age and sex, was obtained for 5-year periods of the census years between 1971 and 1996. The final cohort contained 4305 firemen (4221 male, 84 female). The cancer follow-up time for the cohort was 62366 male person-years and 691 female person-years. The standardised incidence ratio (SIR) for all male cancers combined was not elevated, SIR = 0.95 (0.8-1.1) based on 118 cases. The incidence of male cancer of the kidney was 0.57 (0.1-2.1) based on two cases.

From the point of view of measures of exposure, length of the historical cohort and the length of follow-up, the study of firemen in Philadelphia, 1925 to 1986, conducted by Baris et al., 2001, is particularly valuable. Comparison was made against the general white male population of the USA. The 7789 firemen were normally employed in their late 20s and worked for an average of 18 years, with an average of 26 years follow-up. This provided 204821 person-years of follow-up in which there were 2220 deaths, of which 500 were due to cancer. Thus, this study involved a cancer study population of about 30% the size of Burnett et al., 1994 or Ma et al., 1998. The measures of exposure that were used were:

1. duration of employment ($\leq$ 9 years; 10 – 19 years; $\geq$ 20 years);
2. type of company employment (engine only; ladder only; engine and ladder);

3. year of hiring (before 1935; 1935-1944; after 1944);
4. cumulative number of fire runs (low, ≤ 3323; medium, ≥ 3323 & ≤ 5099; high, > 5099, i.e., less than the median, ≥ median and ≤ 75th percentile, and ≥ 75th percentile);
5. accumulation of fire runs (low, ≤ 3191; high, > 3191);
6. fire runs during first 5 years as a fireman (low, ≤ 729; high, > 729), and
7. lifetime fire runs with diesel exposure (non-exposed; low exposed, 1 – 259 runs; medium exposed, 260 – 1423 runs; high, ≥ 1423 runs).

Risk of mortality from kidney cancer was highest among firemen with at least 20 years service, SMR = 2.20 (1.18-4.08) based on 10 of the overall total of 12 deaths. The publication states that this risk tended to increase with duration of employment, but this is not supported by the data. Year of first employment did not show any strong or consistent pattern, the only period associated with an increased risk of kidney cancer being 1935-1944, SMR = 2.11 (1.06-4.24) based on 8 of the 12 deaths. The risk of kidney cancer was also increased in firemen who worked only in engine crews, SMR = 1.37 (0.62-3.05) based on 6 deaths. No kidney cancer deaths occurred in the ladder crews. Analysis of a slightly reduced set of data for exposure described by the cumulative number of fire runs in any position (fireman, lieutenant or captain), be these designated as low, medium or high, showed no significant pattern associated with kidney cancer mortality. No association with kidney cancer mortality was to be seen when the cumulative runs were divided in to just two categories: low or high. In contrast, there was an increased risk of kidney cancer mortality associated with high numbers of fire runs during the first 5 years of employment, SMR = 2.51 (0.64-9.84) based on 7 out of 10 deaths. Eight of the 10 kidney cancer deaths occurred in crews that were not exposed to diesel, so analysis according diesel exposure was not informative, there being one death in each of the low and high exposed categories.

In addition to the studies listed in Table 1 and described above, there were 3 groups of other publications on cancer epidemiology of firemen that were examined. Of these,

1. Five studies have listed cancers that might include those of the kidney under the headings of either genitourinary or urinary tract cancers (Musk et al., 1978; Eliopulos et al., 1984; Grimes et al., 1991; Giles et al., 1993; Deschamps et al., 1995). Of these, a significantly increased risk of genitourinary cancers was recorded in a cohort of firemen in Honolulu, Hawaii: proportionate mortality ratio, 2.28 (1.28-4.06) (Grimes et al., 1991) and an elevated, but not statistically significant increase was recorded in another cohort in Paris, France: standardised mortality ratio, 3.29 (0.40-11.88), this result being based on just two cases (Deschamps et al., 1995). The three remaining studies showed no remarkable risks for kidney cancer: these being a study in Western Australia: SPMR, 1.08 (0.29-2.76) (Eliopulos et al., 1984) a study in Victoria, Australia: standardised incidence ratio: 1.02 (0.28-2.62) (Giles et al., 1993) and a study in Boston, Massachusetts, with a total of 367 cancer deaths, in which there was a standardised mortality ratio of 0.92 for genitourinary cancers combined (Musk et al., 1978).

2. The following publications did not report kidney cancer (or the incidence of kidney cancer was zero):
Mastromatteo, 1959, with 34 cancer deaths;

Williams et al., 1977, with 58% interviews of 13179 cancer cases in 8 regions of USA;
Feuer & Rosenman, 1986, with 23 cancer deaths;
Hansen, 1990, with 21 cancer deaths;
Heyer et al., 1990, with 92 cancer deaths;
Ide, 1998, with 8 malignancies diagnosed.

3. They were case-control studies on firemen, but examining cancers other than those of the kidney (Morton & Marjanovic, 1984; Sama et al., 1990; Demers et al., 1993; Bates & Lane, 1995; Figgs et al., 1995; Finkelstein, 1995).

Although the afore-mentioned studies are not considered in any detail, neither the first nor the third should be neglected when attempting to reach an evaluation of the risks of kidney cancer amongst firemen. Some are clearly too small to be informative, but some are of similar size to those described in more detail above.

Discussion

The steps that are to be followed in arriving at a conclusion regarding the way that a particular disease should be handled by a compensation authority are:

1. hazard identification, based on an evaluation of the available studies;
2. judgment as to whether it is more likely than not that the exposure is the cause of the disease within that population;
3. consideration of the characteristics of a particular individual to see if that judgment can be applied without modification or whether it should be modified in either direction.

The database consisting of the reviewed studies was interpreted according to widely agreed criteria of causation. These are:

1. Consistency of the observed association;
2. Strength of association
3. Temporal sequence of events;
4. Dose-response relationship;
5. Specificity of the association;
6. Biological plausibility of the observed association;
7. Experimental evidence.

A consistent effect must be seen in several studies in different populations and at different times; no single study can provide definitive evidence for a relationship. The strength of the association (the size of the relative risk) is also important for inference of causality, as is the correct time sequence of exposure and response, and dose-response relationship. Furthermore, the effect should show a specificity following a particular exposure and should be biologically plausible.

The strongest (*sufficient*, in IARC terms) evidence for a causal relationship is when a positive relationship has been established between the exposure and human cancer in studies (note the use of the plural) in which chance, bias and confounding have been ruled out with reasonable confidence. Weaker (*limited*, in IARC terms) evidence for

a causal relationship is when a causal relationship is considered to be credible, but chance bias and confounding cannot be rules out with reasonable confidence. The evidence is considered *inadequate* when there are no data or the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Firemen tend to have a lower mortality rate than the general population, at least during the earlier years of employment. It may be that front line firemen are a work population particularly prone to a healthy worker effect, since it appears that many firemen who develop symptoms early in their careers may be moved to other, non-fire-fighting roles (Guidotti & Clough, 1992). This suggestion is supported by the higher prevalence of non-specific respiratory disease amongst firemen who do not actually fight fires (Peters et al., 1974). According Guidotti, 1995, the healthy worker effect seems to be important during the first 20 years or so of employment, due in large part to a reduction in cardiovascular disease, but tends to disappear with longer employment. Bias of this kind, should it occur, is more likely to affect disease categories other than cancer. It was not observed, however, in the very large study of Burnett et al., 1994. In the study of Baris et al., 2001, the SMR for all causes of death was significantly reduced during the first 9 years and after 20 years of employment, but not in the employment range 10 – 19 years. These changes seemed to be largely due to changes in SMRs for circulatory disease and ischaemic heart disease. Guidotti, 1995, has suggested that the healthy worker effect late in employment is due to the removal of workers (because they become unfit) from exposure to risk factors predisposing them to early mortality.

Another general problem affecting studies with firemen is that risk of disease due to exposures at fires has most probably been underestimated due to consistent misclassification resulting from reliance upon the number of years employed as a surrogate for exposure. Although Guidotti & Goldsmith (2002) specifically do not advise that job assignments or cumulative number of fire alarms to which firemen were assigned be used as measures of exposure (the only practical basis being, in their estimation, duration of employment), Austin et al., 2001 provide evidence that duration of employment results in significant misclassification, only 66% of fire department personnel being 1st line combat fire-fighters and many of these combat firemen moving into non-exposed jobs before the end of their careers. As expected, Austin et al., 2001, found that there was a good correlation between the number of runs to fires and the time spent at fires, so that, clearly, the number of runs would be a better surrogate for exposure than years worked as a fireman. However, it was also found that the number of runs may seriously over- or under-estimate the time spent at fires for individual crews, so that time spent at fires is the preferred surrogate. In one example, two crews had almost identical numbers of fire runs, but one spent 1.72 times longer at fires than the other.

In reviewing the literature covering studies of firemen in different parts of the world, with the intention of applying the results to a particular region, it is as well to be aware that it is difficult to generalise across the occupation how one defines high or low exposure and the consequences of these categories. For example, should exposure of firemen in a low category group be considered in the same light as a fireman in a high category group? In the Baris et al, 2001 study, a low cumulative number of runs in Philadelphia was defined as ≤ 3323, whereas in Tornling et al.,

1994, the highest cumulative run category in Stockholm was > 1000. These are very different exposure experiences, yet the mean duration of employment in the Philadelphia study was 18 years, while 61% of firemen in the Stockholm study continued until retirement, 69% of the total having begun employment before the age of 25 years (mean duration of employment not given). This comparison also highlights the difficulty in using employment time as a surrogate for exposure.

In the Introduction, mention was made of life-style and personal factors that could modify the overall risk of developing kidney cancer: cigarette smoking, over-weight or obesity, diabetes, hypertension and hereditary factors. A survey of smoking among firemen in 1980 in the City of Toronto found that about one-third smoked, a proportion that was considered to be similar to the general population (Bates, 1987). Indeed, not accounting for smoking could actually produce a risk estimate that is lower than the real risk. Delahunt et al., 1995, found that when smoking was accounted for the risk of kidney cancer actually increased. On the other hand, fire fighting is a stressful occupation and there may be important physiological and psychological changes that occur when, at a later stage in the career of a fireman (or when there is a career change) a less demanding daily routine is encountered. While it is unlikely that any firemen would be obese (BMI > 30.0) early in their career, they might easily be in the overweight category (BMI = 25.0-29.9) and weight changes later in life are also important for risk of cancer. Active firemen are expected to be physically fit for their work, in which case differences in blood pressure and BMI between firemen and the general population are likely to drive the risk estimates towards the null, thereby underestimating the effects of employment as a fireman. These factors may have greater importance in assessing the characteristics of an individual case, than those of a population under study.

A strong indication that the occupation of fireman is associated with elevated risk of kidney cancer comes from the case-control study of Delahunt et al., 1995 on 710 kidney cancers because, not only was the occupation identified, but the data were stratified for age and smoking history, resulting in the highly significant risk ratio of 4.69 (2.47-8.93). This is supported by the cohort studies of Baris et al., 2001, who found particularly elevated risks among firemen with ≥ 20 years service, SMR = 2.20 (1.18-4.08) and (although not significant) with a high number of fire runs in the first 5 years of service, RR = 2.51 (0.64-9.84). Lower, yet significant, risk ratios, were obtained in the 24-27 state studies of Burnett et al., 1994 and Ma et al., 1998, with PMR = 1.44 (1.08-1.89) and MOR = 1.3 (1.0-1.7), respectively. These studies are taken together because it is likely that they were not independent populations. The Guidotti, 1993 investigation was, with respect to kidney cancer, of similar size to the Baris et al., 2001 study, and obtained an SMR = 4.14 (1.66-8.53). Finally, Grimes et al., 1991, found a genitourinary tract cancer PMR of 2.28 (1.28-4.06). It is noted, however, that the malignancy groupings in both the Grimes et al., 1991, study and the Guidotti, 1993 study are broader than the kidney alone.

Of the other studies, most showed no excess of kidney cancer, but the numbers were very low (Aronson et al., 1994; Tornling et al., 1994; Bates et al., 2001). Also in this category of very low numbers, Deschamps et al., 1995 found an SMR = 3.29 (0.40-11.88), but this result suffers from being a compilation of genitourinary tract cancers.

Enumeration of the studies shows little difference between those suggesting that fighting fires entails a risk for kidney cancer and those that do not, but the studies supporting the hypothesis are larger and in some cases have information about exposure assessment. None of the studies not supporting the hypothesis is of similar technical standard. Thus, it is believed that the criterion of consistency is fulfilled. These same supportive studies also include strong associations, the relative risk in the case-control study being close to 5, after correction for age and tobacco smoking. Exposure-related responses were indicated in some of the studies. It might be considered that an important weakness in the hypothesis is that a causative agent has not been identified, although some of the atmospheric components of fires have been suspected of increasing the risk of kidney cancer. More important are the weaknesses of proportionate mortality studies, as listed by Burnett et al., 1994: thus, the information on the death certificate may be inaccurate, especially for an occupational group that routinely retires early and may pursue other jobs; there is no information on possible confounders such as tobacco smoking and alcohol consumption; and there is no information on length of employment or possible occupational exposures. Furthermore, the PMR method of estimating risk will overestimate risk if the overall death rate for the occupational group is low, as might be the case for firemen (DeCouflé et al., 1980).

Conclusion

In conclusion, it is considered that there is *limited* evidence that exposures entailed as a fireman do increased the risk of kidney cancer. The evidence is *limited*, not *sufficient*, because of a lack of good exposure assessment in almost all studies. The implication is that there is not, automatically, a "more likely than not" probability (i.e., 50+% probability) that a kidney cancer in a fireman is the result of exposures encountered in his occupation.

An alternative method of arriving at a judgment of "more likely than not" to be due to occupational exposure that has been suggested is the use of the "aetiological fraction," this being the (Relative Risk – 1)/Relative Risk. If the relative risk (RR) is > 2.0 then the requirement for toxic torts is said to have been met (Muscat & Huncharek, 1989)[2]. This criterion has been used more recently in relation to firemen (Guidotti, 1996), but less stringent conditions have also been applied (Guidotti & Goldsmith, 2002, who also quote the Industrial Disease Standards Panel of the Ontario Workers' Compensation Board, 1994). The latter two publications seem to have settled on a Standardised Mortality Ratio of 1.7.

Additional factors may modify the particular situation. These include consideration of the fireman's exposure as defined by:

1. ideally, the length of time the individual spent at fires, or
2. the cumulative number of fire runs for that individual, or

[2] Questions that appear to be left unanswered are whether: (1) the RR itself should be > 2.0, while the magnitude of the 95% confidence interval is of no interest; (2) the RR should have a lower confidence interval that is > 1 and a higher interval that includes 2.0; (3) the RR itself should be > 2.0 and the lower confidence interval should be > 1; or (4) the RR should have a lower confidence interval > 2.0. In the opinion of this reviewer, (1) is too lax and (4) is too stringent, while both (2) and (3) are consistent with the conventional requirement for statistical significance. Which of these is chosen has presumably been determined in the courts.

3. the cumulative number of fire runs for the crew/unit/fire hall(s) in which the individual was employed, or
4. length and category of employment, this being the least suitable exposure surrogate.

These additional factors to be considered also include an individual's personal characteristics, since these may indicate that his risk is greater or smaller than that of the general population.

An important factor for consideration is latency, this being the time between first exposure to the supposed risk factor and clinical diagnosis. In many epidemiological studies, however, the longer time interval between first exposure and death is all that is available. Diagnosis of kidney cancer has tended to be only when the disease is well developed, since it commonly causes no symptoms in early stages. Therefore, although there is a difference in the defined latency depending on whether it is based on diagnosis or death, in renal cancer this difference is likely to be less than for many other solid tumours. A rule of thumb that is often adopted is that the latency for a solid tumour is about 20 years, with the understanding that there is a variation around this figure and that it can be shortened under the influence of a strong exposure. A better reflection of the latency of a particular tumour type in particular exposure circumstances can probably come from epidemiological studies that are directly relevant. In the case of kidney cancer amongst firemen, there are two better sources of this information: the mortality studies of firemen in Alberta (Guidotti, 1993) and Philadelphia (Baris et al., 2001). In Alberta, out of a total of 7 cases, no cancers of the kidney (or ureter) occurred below the age of 40 and the earliest case was observed 18 years after entry to the service. Maximum risk was observed 40-49 years after entry (note that, although service time may be a surrogate for exposure, it is the least satisfactory measure amongst this those possibilities listed above) and one case had no exposure to fires. In Philadelphia, out of a total of 12 cases, 2 occurred after ≤ 9 years, but this incidence was similar to the expected standardised mortality (SMR = 0.72, 95% CI 0.18 – 2.87); none occurred in the employment range 10 – 19 years; and the remaining 10 cases occurred after ≥ 20 years of service. This last represented a statistically significant increase as well as meeting the criterion of "more probably than not" being due to the risk factors experienced (SMR = 2.20, 95% CI 1.18 – 4.08). From these relevant data, it would appear that kidney cancers amongst firemen are more likely to be due to occupational exposures if they should occur after employment for 20 years or more. The considerations specific to an individual, as listed above, should always be applied in any particular case.

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•Table 1. Summary characteristics and results of studies on the relation between occupational exposure as a fireman and cancer.

Reference	Study base & type	Reference group	Numbers	Risk* (95% C.L. or significance level)	Adjustments & Comments
Musk, et al., 1978	Firemen in Boston, MA Cohort 1915-75	Massachusetts men	5655 firemen with 367 cancer deaths	Urogenital combined SMR = 92, n.s.	No dose-response analysis. Based on death certificates. 104561 person-years actively working; 38414 person-years retirees
Eliopulos et al., 1984	Firemen in Western Australia, 1939-78	Western Australia men	990 firemen with 30 cancer deaths	All cancers, SMR = 1.09 (0.74-1.56) Urogenital, SPMR = 1.08 (0.29-2.76)	No dose response analysis. Based on death certificates. 16876 person-years
Vena & Fiedler, 1987	Firemen in Buffalo, NY, 1950-1979	White USA men	102 cancer deaths	All cancers, SMR = 1.09 (0.89-1.32) Kidney, 3, SMR = 1.30 (0.26-3.80)	Gradiant in the SMR with years of service for all cancers, colon and urinary bladder. Not corrected for age. 32858 person-years
Beaumont et al., 1991	Firemen in SanFrancisco, California, 1940-82.	White USA men	3066 firemen with 236 cancer deaths	All cancers, SMR = 0.95 (0.84-1.08) Kidney, 4, SMR = 0.68 (0.19-1.74)	Analysis of dose-response inconclusive. Number of person years not stated.
Grimes et al., 1991	Firemen in Honolulu, Hawaii, 1969-88.	Hawaii men	205 deaths, including 58 cancer deaths.	All cancers, PMR = 1.19 (0.96-1.49) Urogenital, PMR = 2.28 (1.28-4.06)	Proportionality study. Small numbers of individual cancers. No analysis of dose-reponse.
Demers et al., 1992	Firemen in Seattle, Tacoma & Portland, NW USA, 1945-89	Police in the same cities (p). White USA men (m)	4401 firemen with 291 cancer deaths	All cancers, IDRp = 0.97 (0.67-1.33) SMRm = 0.91 (0.85-1.07) Kidney, IDR = NR SMR = 0.27 (0.03-0.97)	122852 person-years for the 3 cities
Giles et al.,1993	Firemen in Melbourne, Australia, 1980-89	Men in Victoria	2865 firemen, 50 cancer cases	All cancers, 50, SIR = 1.13 (0.84-1.48) Urinary tract, SIR = 1.02 (0.28-2.62)	20853 person-years of observation. Dose-response analysis non-significant
Guidotti, 1993	Firemen in Edmonton & Calgary, Alberta, 1927-87	Men in Alberta	3328 firemen with 92 cancer deaths	All cancers, 94, SMR = 1.27 (1.02-1.55) Kidney, 7, SMR = 4.14 (1.66-8.53)	Follow-up of 96% of the cohort for 64983 person-years. Weighting of years of service with job category time at fires estimates: fireman lieutenant, captain = 1; safety/training = 0.2; district chief = 0.1; desk job = 0.0. Dose-response analysis inconclusive
Aronson et al., 1994	Firemen in Toronto, Ontario, 1959-89	Men in Ontario	5414 firemen with 199 cancer deaths	All cancers, 199, SMR = 1.05 (0.91-1.20) Kidney, 2, SMR = 0.43 (0.05-1.56)	114008 person-years of follow-up. Dose response analysis non-significant. No information on smoking habits or diet.
Burnett et al.,	Firemen in 27 states of	Men who died in	Number of	All cancers, 1636,PMR = 1.10 (1.06-1.14)	Proportionality study. Large number of

1994	the USA, 1984-90	the same 27 states of USA	firemen not stated. 1636 cancer deaths	< 65 years age, 663, PMR = 1.12 (1.04-1.21) Kidney, 53, PMR = 1.44 (1.08-1.89) <65 years age, 24, PMR = 1.41 (0.90-2.10)	cases, but no information on possible confounders, length of employment or occupational exposures.
Demers et al., 1994	Firemen in Seattle & Tacoma, NW USA, 1974-89.	Police in the same cities (p) Men in the same counties (m)	2447 firemen with 244 cancer deaths	All cancers, SIRp = 1.0 (0.8-1.3) SIRm = 1.1 (0.9-1.2) Kidney, SIRp = 0.4 (0.1-2.1) SIRm = 0.5 (0.1-1.6)	Sub-group of the preceding study . Small numbers for some cancers
Tornling et al., 1994	Firemen in Stockholm, Sweden, 1951-86	Men in the Stockholm region	1116 firemen with cancer incidence of 127 and 93 cancer deaths	Incidence: All cancers, 127, SMR = 1.00 (0.83-1.19) Kidney, 2, SMR = 0.36 (0.04-1.29) Mortality: All cancers, 93, SMR = 1.02 (0.88-1.25) Kidney, 4, SMR =1.10 (0.30-2.81)	Tendency for a dose-response relationship between incidence of all malignant tumours combined and age, duration of employment and number of fires attended.
Delahunt et al., 1995	Register-based case-control study of kidney cancer in New Zealand, 1978-86	12756 cases of cancers at other sites in the register in the same period	914 cases (710 men)	Kidney, RR = 4.69 (2.47-8.93)	Adjustment of tobacco usage status only available in the register
Deschamps et al., 1995	Firemen in Paris, France, 1977-91	Men in the general population of France; age and cause-specific cancer rates	830 firemen with 18 cancer deaths	All cancers, 18, SMR = 0.89 (0.53-1.40) Genito-urinary, 2, SMR = 3.29 (0.40-11.88)	
Ma et al., 1998	Mortality odds ratio study of death certificates of firemen for race-specific cancer risk in 24 states of USA, 1984-93	Men who died from causes other than cancer	6607 deaths of firemen with 1883 cancer deaths (1817 white, 66 black)	**WHITE**: All cancers, 1817, MOR = 1.1 (1.1-1.2) Kidney, 49, MOR = 1.3 (1.0-1.7) **BLACK** All cancers, 66, MOR = 1.2 (0.9-1.5)	Small numbers for some cancers in whites, small numbers for most cancers in blacks, leading to instability of the MORs. Database similar to Burnett et al., 1994, but extended by 3 years and 3 states not included; similar strengths and weaknesses.
Bates et al., 2001	Historical cohort study of all firemen in New Zealand, 1977-95	Men who died from cancer in the same period throughout New Zealand	4221 firemen	All cancers, 118, SIR = 0.95 (0.8-1.1) Kidney, 2, SIR = 0.57 (0.1-3.0)	58709 person-years. Data do <u>not</u> include 2/4 testicular cancer cases occurring in the Wellington cluster (Bates & Lane, 1995) Results (notably for testes) not changed by analysis for 1990-96 period (Cancer Registry database more complete from about 1990)
Baris et al., 2001	Historical cohort mortality study of	Men in the general USA population	7789 firemen with 2220	All cancers, 500, SMR = 1.10 (1.00-1.20) Kidney, 12, SMR = 1.07 (0.61-1.88)	204821 person-years of follow-up. Thus, the largest study available to date.

	Philadelphia firemen employed 1925-86		deaths	**Duration of employment:** ≤ 9 years Kidney, 2, SMR = 0.71 (0.18-2.87) 10 – 19 years Kidney, 0 – ≥ 20 years Kidney, 10, SMR = 2.20 (1.18-4.08) **Year of hiring (1925-1986)** Before 1935 Kidney, 2, SMR = 0.57 (0.14-2.29) 1935-1944 Kidney, 8, SMR = 2.11 (1.06-4.24) After 1944 Kidney, 2, SMR = 0.50 (0.12-2.01) **Cumulative number of runs** Low (<3323 runs) Kidney, 4, SMR = 1.18 (0.44-3.15) Medium (≥3323 & <5099 runs) Kidney, 4, SMR = 1.90 (0.71-5.07) High (≥5099 runs) Kidney, 2, SMR = 0.89 (0.22-3.55) **Runs during first 5 years as fireman** Low (≤729 runs) All cancers, 171, RR = 1.00 Kidney, 3, RR = 1.00 High (>729 runs) All cancers, 169, RR = 1.05 Kidney, 7, RR = 2.51 (0.64-9.84)	Best estimates of exposure because, in addition to duration of employment, the cohort was analysed according to job assignment and – most importantly – number of runs.

*I.D.R. = incidence density ratio; M.O.R. = mortality odds ratio; O.R. = odds ratio; R.R. = relative risk; S.I.R. = standardised incidence ratio; S.M.R. = standardised mortality ratio; S.P.M.R. = standardised proportional mortality ratio